Ethical issues in the design and conduct of cluster randomised controlled trials

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In most randomised controlled trials, individual patients are randomised to a treatment or control group, but sometimes this is undesirable or even impossible and groups (clusters) of people may be randomised instead. These are called cluster randomised controlled trials, and although they have been around for a long time, the need for them is likely to increase in line with growing concern to evaluate the delivery of health services, public education, and policy on social care.

Summary points

- Need for cluster trials will increase with concern over health service evaluation, but issues of ethics and guardianship must be addressed
- In some cluster trials the intervention can be targeted at individuals (individual-cluster); where this would be too difficult or expensive the intervention is targeted at the whole group (cluster-cluster)
- Autonomy is important in individual-cluster trials, while the utilitarian welfare of the cluster as a whole is of paramount importance in cluster-cluster trials
- In individual-cluster trials the participants should give consent; cluster-cluster trials need procedural safeguards appropriate to the risks carried by the cluster intervention
- Guardians should sign a consent form that sets out their duties before they volunteer a cluster for a trial

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BMJ 1999;318:1407–9

Ethical context

The ethical aspects of medical practice and medical research are most often discussed in the context of two main moral traditions—utilitarianism and Kantian ethics. Broadly speaking, utilitarianism is concerned with increasing social utility (value), which usually means that the individuals maximise their expected utility and so act in their own best interests. In the long run social utility will not be served by demanding that individuals be self sacrificing for the common good. This leads to matters of distributive justice whereby utility and disutility, benefits and costs, are distributed as fairly and evenly as possible across society. The Kantian tradition shows why we are duty bound to respect a person's autonomy.

There is some harmony between these traditions as competent patients are in the best position to know how they value possible consequences (utilities) and, equipped with the relevant probabilities, they are best placed to make decisions that concern them directly.[1] This takes the form of informed consent from individual participants. In cluster randomised controlled trials, however, informed consent for trial entry (that is, for randomisation) cannot be obtained individually because one person's choice will impinge on another's. The question then is, under what, if any, circumstances are cluster trials ethical? Here we discuss why a cluster trial might be mounted, who has a duty of care to the people who form the cluster in question and should make the decision to participate on its behalf, and how this duty of care should be discharged.

Why randomise by cluster?

There are two widely used arguments for randomisation by cluster. Firstly, the intervention itself may be administered to and affect entire clusters of people as opposed to individuals within that cluster. Examples include interventions that are diffuse (for example, information technology) or area wide (for example, promoting lifestyle changes on local radio). Secondly, although the intervention or treatment is given to individuals, it may also affect others within that cluster. This may be because it "leaks," contaminating those who are not supposed to receive it, thereby weakening any estimate of treatment difference. For example, people who are receiving a behavioural intervention to reduce smoking may talk it over with control subjects, who may in turn adopt the experimental practice. Some interventions, despite being limited to individuals, may affect others through a "herd effect." For example, people in a cluster that has been vaccinated not only have more resistance to the illness against which they have been vaccinated, but they are also less likely to be exposed to the illness in the first place.

Who consents to trial entry?

In the normal research process, a researcher (trialist) and sponsor decide to launch a trial; they are generally

interested in the scientific results of the trial, perhaps to influence policy. However, the decision about whether a particular cluster participates in the trial is taken by an agent, whom we call a guardian and who has the power to "deliver" that cluster. Examples of guardians include the chief executive of a hospital, managing partner of a primary care practice, or head teacher. Guardians may be democratically elected or appointed, though not necessarily with this specific role in mind. In deciding to volunteer the cluster for an experiment that is not routine, the guardian, as advocate, must act in the best interests of the cluster; this may or may not be his or her habitual role. It should be noted that guardians, like doctors in conventional trials, have some potential conflicts of interest. They may, for example, have a scientific interest in the results as well as a benevolent concern for the welfare of the cluster, or they may receive financial incentives. Consequently, safeguards, like ethics committee approval, are desirable.

In this article, we consider the usual situation where a guardian is in a position to volunteer a cluster for a trial. A different situation would arise if a policy maker rather than a researcher decided to introduce a change in service delivery around an evaluative and possibly a cluster framework. Policy makers would be acting as researchers, but might also put clusters of people into a trial without seeking guardian consent or, indeed, without any further consultation.[2] Although this situation seldom arises in current policy making, it may become more widespread, and we will discuss its ethical implications in a future paper.

How should researchers and guardians decide to initiate or enter a group in a cluster randomised controlled trial? This depends on why the cluster trial is being conducted. If the intervention itself is a cluster one, individuals cannot act independently, in which case the guardian needs to consent to the intervention as well as to trial entry. However, if the individuals within clusters are given treatments, they can in theory consent individually to the treatment(s) offered within their cluster. Here, ethical problems may arise if details about the treatment are withheld solely to avoid trial contamination. Thus, in moral terms, there are two types of cluster trial, and for ease of reference we will call these cluster-cluster trials and individual-cluster trials.

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Evaluating cluster interventions

As we have seen, cluster interventions themselves, and not just decisions about trial entry, affect whole clusters of people, and individuals cannot therefore decide or act independently. The decision to implement all cluster interventions may be construed as a paternalistic one. Similarly, the decision not to implement a cluster intervention may be paternalistic. Sometimes the intervention cannot be targeted at an individual—for example, health promotion on local radio, instituting a system of clinical audit, or providing clinicians with extra education. In other cases, the intervention could be given to individuals, but this would be very difficult in practical terms, or extremely expensive. For example, it would be possible to pipe water to individual households in order to evaluate the effects of fluoridating water, but only at vast expense. Thus, the distinction between cluster-cluster trials and individual-cluster trials is not always clear cut. Sometimes, people who object strongly to specific cluster policies find ways of deliberate non-compliance. For instance, an individual cannot refuse to have fluoride added to his or her water supply, but may choose to drink bottled water instead. As a rule of thumb, the more readily a treatment can be targeted at individuals, the easier it is for someone to avoid it.

The guardian should only volunteer his cluster when trial entry would be in its best interests. This would mean that the expected utility of the trial intervention is greater than that of the alternatives—that is, the default or non-trial option. Questions on how to quantify the best interests of a group remain, but this is a problem for all decisions concerning cluster interventions, whether in a trial or not. These calculations should include all the considerations of distributive justice, utility, and equity that would be brought into play when making policy decisions generally. If the intervention is controversial or culturally sensitive, it may be prudent, or even necessary, to preserve trust by consulting members of the cluster in question by way of an opinion poll, by consulting community representatives, or by forming focus groups or citizens juries.[3] Referendums could be held, too, but may only be deemed necessary by an ethics committee in extreme cases. In short, the procedural safeguards should be commensurate with the perceived risks. In cluster-cluster trials, the autonomy prinicple is lost except insofar as the individual has any democratic choice of who the guardian is and some right to consultation by the guardian. However, this is not guaranteed and it makes the utilitarian principle the more important.

Evaluating individual interventions

In the case of cluster-cluster trials, therefore, a guardian must consent to or decline both trial entry and the intervention as a single package. In the case of individual-cluster trials, however, it is only trial entry that takes place without individual consent, as the individual treatments offered can be declined or accepted

by each participant. This resembles a conventional trial where consultation over consent implies that available alternatives are offered and that these always include routine care. The same is ethically required for individual-cluster trials, where consent helps ensure that no individual loses out prospectively and the intervention group has more treatment choices. A cluster trial of a routine vaccine versus an experimental vaccine, for example, would give people in the experimental arm a chance of selecting their care from an extended treatment list. Of course, on this basis it would be unethical for a guardian to offer only the experimental vaccine, if assigned, without giving individuals all the options available routinely. This makes it difficult, if not impossible, to use individual-cluster trials to compare two treatments that are both already routine.

But what about controls? The scientific reason for carrying out an individual-cluster trial is often to avoid contamination. Informing controls fully about the experimental arm(s) is likely to produce the very effect that randomising by cluster was designed to avoid—that is, prompting controls to adopt the treatment(s) under investigation. One option is to withhold information about the novel treatment from controls, on the grounds that they are getting conventional care and are therefore in the same position as people outside the experiment. This is reminiscent of the Zelen design, used occasionally in conventional settings to avoid bias or distress among controls. Here individual consent to the experimental treatment and participation is sought from those in the experimental arm only after randomisation has taken place. The controls receive routine care and do not know that they could have been offered the experimental treatment.[4] A pragmatic distinction can thus be drawn between withholding information from controls in conventional and cluster settings, respectively. In the former, the clinician is withholding information that is likely to be in his mind, given that he will have treated other patients differently. In the latter, the clinician treats all patients in the same way. Whether this argument will prove acceptable to guardians and the public can only be tested empirically.

If this option turns out to be unacceptable (even though routine records are sometimes used without patient consent in other contexts)[5] or if personal follow up is required, assent to study participation could be sought from all individuals, without their first knowing the precise nature of the novel treatment. By assenting, individuals would be expressing trust in the guardian as their advocate. Ethics committees seem to be in a good position to decide whether or not assent should be required, and to judge whether an individual-cluster trial can yield scientifically valuable data at the same time as protecting individual participants' rights.

Conclusion

In cluster-cluster trials, the welfare of the cluster as a whole must be considered, and we find no ethical difficulty with cluster-cluster trials as such, but recommend that procedural safeguards should be commensurate with the risks that the particular cluster intervention carries (in trial as in non-trial practice). The essential point about individual-cluster trials, by contrast, is that individuals can and should give their consent to any experimental treatment, and they should always be offered routine care. We suggest participant "assent" where controls are to be followed up personally, but where there is a risk that fully informing controls will contaminate them. Assent may be regarded as a necessary requirement, even if personal follow up is not envisaged. We conclude that the role of guardian is key to the ethical conduct of cluster trials, and we suggest that guardians should sign a consent form clearly setting out their duties before volunteering a cluster. In the longer run, individual autonomy could be strengthened by considering the rights of individuals vis à vis the selection and behaviour of cluster guardians.

Competing interests: None declared.

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(Accepted 10 February 1999)

One hundred years ago

Is nail-cutting a surgical operation?

Some time ago a German court had to adjudicate on the question whether corns constitute a disease. A still more abstruse problem has recently engaged the attention of a Vienna tribunal. A medical practitioner of that city, having occasion to operate, very properly trimmed his nails as a preliminary. In doing so, however, he cut his finger, but was nevertheless able to perform several operations on the same day. The wound became infected, and the practitioner himself had to be operated on. He was thus disabled for twenty-one days, and therefore claimed 5 florins a day from an accident assurance company. The company repudiated liability, on the ground that, according to its by-laws, no claim can be entertained for an operation performed by a medical practitioner on himself.

The question whether nail-cutting is a surgical operation appears to have proved too much for the judicial intellect, for, after hearing arguments on both sides and suffering much vexation of spirit, the court reserved its decision. We do not presume to offer any help towards the solution of so subtle a question. We venture, however, to submit that, if nail-cutting comes within the sphere of operative surgery, *a fortiori* shaving must do so, for that procedure was once among the duties of a surgeon. So well was this recognised in some countries that at the beginning of the present century some English surgeons were summarily dismissed the Danish Naval Service for refusing to act as barbers to the crews of their ships. (*BMJ* 1899;ii:1377)